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FeNO in Asthma

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Abstract

Asthma is a common disease affecting 350 million people worldwide, which is characterized by airways inflammation and hyperreactivity. Historically diagnosis and treatment have been mainly based on symptoms, which have the potential to result in misdiagnosis and inappropriate treatment. Nitric oxide (NO) is exhaled in human breath and is a marker of airways inflammation. Levels of NO are increased in the exhaled breath of patients with type 2 asthma and fractional exhaled nitric oxide (FeNO) provides an objective biomarker of airway inflammation. FeNO testing is an accessible, noninvasive, and easy-to-use test. Cut-off values have been established by the American Thoracic Society (ATS), the Global Initiative for Asthma (GINA), and the National Institute for Health and Care Excellence (NICE) but vary between guidance. FeNO levels have been shown to be predictive of blood and sputum eosinophil levels but should not be used in isolation and current guidance emphasizes the importance of incorporating clinical symptoms and testing when utilizing FeNO results. The inclusion of FeNO testing can increase diagnostic accuracy of asthma, while high levels in asthmatic patients can help predict response to inhaled corticosteroids (ICS) and suppression of levels with ICS to monitor adherence. FeNO levels are also a predictor of asthma risk with increased exacerbation rates and accelerated decline in lung function associated with high levels as well as having an emerging role in predicting response to some biologic therapies in severe asthma. FeNO testing is cost-effective and has been shown, when combined with clinical assessment, to improve asthma management.

Keywords

- asthma
- biomarkers
- diagnosis
- fraction of exhaled nitric oxide
- management
- monitoring
- type 2 inflammation

Asthma is a chronic disease characterized by airway inflammation, hyperresponsiveness, and remodeling. This leads to respiratory symptoms and airflow limitation that typically varies in both time and intensity.[1] Its heterogenous nature and temporal variability can make asthma difficult to diagnose and treat. Furthermore, asthma is common with more than 350 million people estimated to have asthma worldwide[2] including 25 million people in the United States (7.8% of the population).[3]

The diagnosis of asthma historically centers on clinical symptoms; however, many other diseases have similar symptoms, leading to both the under- and overdiagnosis of asthma.[1,4] In a Canadian study, one-third of patients diagnosed with asthma in the preceding 5 years were found not to have asthma when undergoing objective testing,[5] a proportion consistent with other published data.[6–8] Similarly, asthma management focuses on symptom control,[1] but symptoms are not always predictive of future risk.[9,10] Objective measurements of lung function and airway inflammation, such as fractional exhaled nitric oxide (FeNO), are therefore needed to improve diagnosis, phenotype patients, and guide treatment in asthma.[5,11]

Asthma is a heterogenous disease consisting of multiple overlapping phenotypes driven by different endotypes.[12–15] Identifying these phenotypes, including the broad definition of type 2 and non–type 2 asthma,[16] allows better understanding of disease mechanisms and the personalization of treatment.[11,15] Type 2 inflammation in asthma is driven by enhanced IL-4, IL-5, and IL-13 cytokine production from T helper 2 (Th2) and innate lymphoid type 2 (ILCs)

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cells. This results in eosinophilic inflammation, goblet cell hyperplasia, airway hyperresponsiveness, and immunoglobulin E (IgE) production.[17] Type 2 asthma tends to be associated with allergic and/or eosinophilic asthma, responding to corticosteroids[18] and is targeted by current biological therapies.[19–23] It is thought to be present in a large proportion of children and at least 50% of adults with asthma[24]; however, this number is thought to be an underestimate with corticosteroid withdrawal often revealing type 2 inflammation.[25] Biomarkers including FeNO, blood and sputum eosinophils, and serum IgE can help identify type 2 inflammation and indicate the underlying mechanisms that are driving symptoms.[26–28] Asthma management typically focuses on reducing inflammation through inhaled corticosteroids (ICS) with decisions to increase or stepdown therapy also based on patient symptoms. However, this approach fails to consider objective markers of airway inflammation and thus individual phenotypes to personalize therapy.[11]

FeNO can be regarded as an indirect marker of IL-13-mediated type 2 airway inflammation,[29,30] and is the only licensed point-of-care test for type 2 inflammation in asthma.[31] FeNO levels can be quantified safely in children and adults through portable, noninvasive devices that are relatively easy to use and allow for repeated readings over time.[1,29,32] A raised FeNO in combination with a clinical history, spirometry, and other biomarkers can aid with asthma diagnosis, predicting responsiveness to ICS and stratifying add-on biologic therapies in severe asthma.[1,29,33,34]

The Biology of Nitric Oxide

Nitric oxide (NO) is a gaseous molecule found in the respiratory and cardiovascular systems of humans.[35,36] All humans exhale NO in their breath, in healthy individuals 40–45% of airway NO is produced in the lower respiratory system with the remainder originating from the upper respiratory tract.[37] NO is a modulator of type 2 inflammation and is increased in the exhaled breath of many asthmatics with its concentration widely recognized as marker of airway inflammation.[38,39]

NO is produced in an enzymatic process which uses NO synthase (NOS) to convert L-arginine to L-citrulline and NO; it is dependent on both oxygen and NADPH (►**Fig. 1**.)[40] There are three isoforms of NOS, originally referred to as inducible (iNOS) or constitutive (cNOS) forms of NOS with the constitutive forms named according to their site of expression. However, they are now known to be expressed from several cells and cNOS is also classified as NOS1 and NOS3, while iNOS is known as NOS2.[41] Activation of cNOS occurs in response to a calcium signal producing basal levels of NO from rapid but short-lived activation and production of NO.[37] They are corticosteroid resistant meaning that basal release of NO is not influenced by steroids.[42–44] In contrast, iNOS is produced in response to the inflammatory cytokines: interferon-γ, interferon 1-β, and tumor necrosis factor-α. It has also been suggested that IL-13 upregulates gene expression and transcription in epithelial cells to promote iNOS. In contrast to cNOS, NO production through iNOS is a sustained process independent of calcium[37] producing significantly

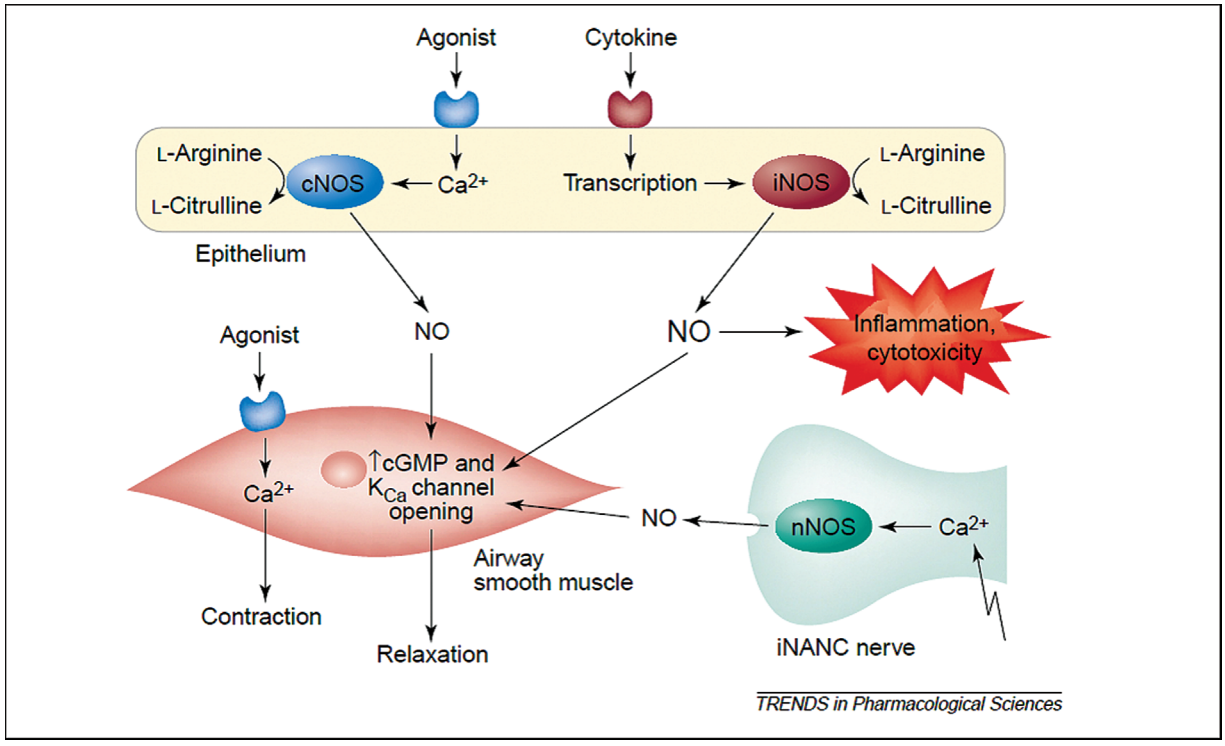

Fig. 1 Production of nitric oxide in asthma. cGMP, cyclic guanosine monophosphate; cNOS, constitutive nitric oxide synthase; iNANC, inhibitory nonadrenergic noncholinergic; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase; NO, nitric oxide. (Source: Meurs H, Maarsingh H, Zaagsma J. Arginase and asthma: novel insights into nitric oxide homeostasis and airway hyperresponsiveness. Trends in Pharmacological Sciences 2003;24:450–455.)

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higher concentrations than those seen by cNOS1 activity.[41] It is therefore the production of NO by iNOS that is clinically relevant when measuring FeNO and in relation to asthma.

Healthy airway epithelium has been observed to have iNOS,[42] but expression is significantly upregulated in asthmatic airways mainly in epithelial and inflammatory cells such as eosinophils, neutrophils, and macrophages.[45,46] NO acts as a messenger molecule and its activity depends on factors such as oxidative stress, antioxidants, and the amount and activity of NOS.[45] It has complex roles in smooth muscle relaxation, vasodilation, and as a neurotransmitter and inflammatory mediator.[47] However, the response is complex. While FeNO is conventionally used as a marker of eosinophilic airway inflammation in asthma, NO also functions as an endogenous bronchodilator.[48,49] In a recent pilot, low FeNO levels in obese people with asthma were augmented with L-citrulline supplementation to increase endogenous NO concentrations. The authors found that L-citrulline supplementation resulted in an increase in FeNO and was associated with improved lung function and asthma control in this patient population.[50] On the other hand, high NO can be deleterious in asthma amplifying the inflammatory response and causing airway hyper responsiveness.[47,51] FeNO levels thus do not only increase with type 2 asthma but with disease severity and exacerbations.

The use of chemiluminescence analyzers has allowed for the detection and measurement of NO in exhaled breath (FeNO). The analyzers have been shown to provide reproducible and stable results over time.[52] Furthermore, they are noninvasive, can be used in children as well as in adults, and provide comparable results in portable devices which lend themselves to remote monitoring.[29,52,53] FeNO testing has now become common place in specialist settings and has been increasingly adopted in primary care.[54] It has been integrated into national and international asthma guidelines[1,29,33,55–57] and is used alongside clinical and other objective testing in asthma diagnosis,[29,33] predicting response to ICS treatment[58] and to monitor adherence.[53]

FeNO as a Biomarker of Airway Inflammation

Biomarkers provide a measurable indicator of normal physiological or pathological responses or the response to a therapeutic intervention.[59] An effective biomarker should be able to distinguish between health and disease, predict future risk, and response to treatment. It should also be easy to use in the real-world setting, reliable, and cost-effective.[60] Such biomarkers are important in asthma, as they allow for the phenotyping of asthma and stratification of treatment.[11,26–28] Several different biomarkers have been identified for type 2 inflammation including serum IgE, FeNO, and eosinophil counts in the blood and sputum.[61]

Given the requirement to accurately assess inflammation in the lung, gold standard assessments of type 2 airways inflammation have traditionally focused on eosinophil counts in induced sputum or bronchial biopsies.[62–64] However, these tests require specific expertise, resources, and do not lend themselves to continued monitoring, limiting their everyday clinical use.[27] FeNO can provide an additional indicator of type 2 airway inflammation that is noninvasive, repeatable, and safe and can be delivered at the point of care.[29] An observational study comparing surrogate markers for sputum eosinophilia found blood eosinophils and FeNO to have comparable diagnostic accuracy, which was superior to total serum IgE in adult asthma patients. This was irrespective of subphenotypes such as severity, atopy, smoking-related asthma, and obesity.[65] Studies elsewhere have, however, shown that obesity can be associated with low FeNO levels even in the presence of sputum eosinophilia.[66,67] FeNO is also associated with eosinophilic inflammation of bronchial tissue.[68] Endobronchial biopsies were examined in children with difficult-to-treat asthma following 2 weeks of oral corticosteroids (OCS) and controls. A significant association was found between FeNO level and the presence of eosinophils ($r = 0.67$, $p = 0.001$), particularly in the presence of symptoms despite OCS. None of the patients with FeNO <7 ppb (parts per billion) had tissue eosinophils consistent with asthma.[68] It is also important to note that FeNO correlates with type 2 airways inflammation, while blood eosinophils are from the systemic circulation and may reflect different aspects of a patient's disease and treatment. For example, FeNO has been shown to be reduced with ICS,[41,69] while the effect on peripheral blood eosinophils is thought to be weak.[70] Conversely peripheral blood eosinophils are affected more by OCS treatment than FeNO.[71]

Both eosinophils and FeNO result from the same type 2 inflammatory cascade; however, they are regulated and produced by different inflammatory pathways (IL-5 and IL-13, respectively).[61] This means it is important to recognize their role as independent biomarkers with different causes and associated outcomes as well as their additive use to create a more holistic picture.[56]

Measuring FeNO

American Thoracic Society (ATS)/European Respiratory Society (ERS)[55] guidelines and a technical standard[72] have been produced for the standardized measurement of NO from the lower respiratory tract. NO levels are measured in a single breath exhaled directly into the analyzer at 50 mL/s for at least 6 seconds in children older than 12 years and adults and for at least 4 seconds for children younger than 12 years. The flow rate is regulated by exhaling against an expiratory resistance, often while a computer graphic provides feedback to the subject. Repeated, reproducible exhalations should be performed to so that two values agree within 10% of each other. The mean of those two values is then recorded as the FeNO. The exhaled NO levels are measured in ppb and can be obtained in real time.[55]

FeNO levels can be influenced by several factors and should always be interpreted in the clinical context. The ATS has set out minimum reporting requirements when performing FeNO to include date, time of the day, age, sex, ethnicity, height, smoking status, reason for the test, prior diagnosis (if known), and use of inhaled or OCS at the time of

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testing. Information should also be available on the device used to make the measurement, the number of measurements made, and the flow rate (currently approved FDA devices use 50 mL/s flow rate). One can choose to include all measurements performed or just the mean value. Results of previous testing (if available) should be included. A listing of the relevant cut-point values is usually helpful.[29]

Interpretation of FeNO Values

Raised FeNO levels have been shown to be associated with type 2 asthma and active airway inflammation but may not always be elevated in asthma.[54] Levels can be used to guide diagnosis,[29] ICS therapy,[33,58] monitor adherence,[53] and guide biological therapies.[22]

The ATS guidelines define high, intermediate, and low FeNO levels in adults as >50 ppb, 25 to 50 ppb, and <25 ppb, respectively. While in children, high, medium, and low FeNO levels are described as >35 ppb, 20 to 35 ppb, and <20 ppb (►**Table 1**).[29] These guidelines emphasize the importance of clinical context when interpreting values and the use of cut-offs rather than reference values based on the "normal population."[29] This is because the values seen in patients with asthma and eosinophilic inflammation (from sputum eosinophilia) overlap with the upper limit of "normal" on nonasthmatic individuals. Instead, the ATS guidance recommends the use of cut-offs, which should be interpreted according to respiratory symptoms and the clinical context.[29]

The Global Initiative for Asthma (GINA) uses a lower cut-off of ≥ 20 ppb in the classification of asthma with type 2 inflammation.[1] However, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidance defines a positive FeNO as a level of >40 ppb in adults and >35 ppb in children (►**Table 1**).[33] The Scottish Consensus defines cut-offs according to steroid exposure with positive values of >40 ppb in steroid-naive patients and >25 ppb for patients on ICS[56] (►**Table 1**).

Changes in FeNO over time are also important and FeNO measurements should always be compared with previous measurements.[29] The ATS describes a change of ≥20% and more than 25 ppb (20 ppb in children) to be potentially significant; for example, a reduction of ≥20% in a previously elevated FeNO 2 to 6 weeks after the initiation of ICS indicates successful reduction in airway inflammation.[29] For initial values of less than 50 ppb, a variation of 10 ppb or more may also be regarded as significant.[29] Although FeNO levels are elevated in patients with type 2 asthma, there is clearly variation in the "positive" cut-off FeNO values among guidelines. This is likely related to the problematic nature of "normal" reference values for FeNO and the multiple factors that can increase or decrease FeNO levels.

FeNO increases with age,[73] height, and sex (although the third may be confounded by height) and also related conditions such as atopy, allergic rhinitis, eosinophilic bronchitis, and rhinovirus in healthy people.[74] Diet also has an effect on FeNO and levels can be temporarily raised by more than 60% by eating nitrogen-rich foods, such as lettuce[75] (►**Table 2**). Conversely, smoking,[74] corticosteroids,[76] and bronchoconstriction[77] lower FeNO levels, a factor reflected in some guidelines (►**Tables 1** and **2**). Reduced FeNO levels can be associated with increasing body mass index (BMI), and particularly obesity, despite sputum eosinophilia, suggesting that lower cut-offs may be required to detect type 2 airway inflammation in obese patients.[66] FeNO can also alter according to the time of day. Anderson et al also found significant diurnal variation of FeNO, almost always higher in the morning in the second week after stopping ICS (amplitude = 15.6%, $p = 0.004$).[76] It is therefore important to always interpret FeNO results within their circumstantial and clinical context.

Clinical Utility of FeNO

Diagnosis of Asthma

FeNO can provide a noninvasive adjunct for the initial diagnosis of asthma with the ATS[29] and NICE[33] recommending it as part of their current guidelines and diagnostic algorithms. It is, however, important to note that interpretation of FeNO results depends on the pre-test probability of an

Table 1 FeNO cut-offs according to guideline

	Adults	Children
ATS (2011)	High: >50 ppb Intermediate: 25–50 ppb Low: <25 ppb	High: >35 ppb Intermediate: 20–35 ppb Low: <20 ppb
GINA (2021)	≥ 20 ppb	
NICE (2017)	>40 ppb	>35 ppb
Scottish Consensus (2019)	>40 ppb ICS-naive patients >25 ppb patients taking ICS	

Abbreviations: ATS, American Thoracic Society; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; NICE, National Institute for Health and Care Excellence.

Table 2 FeNO level confounders

FeNO levels increased with:	FeNO levels reduced with:
Allergic rhinitis[126]	Reduced age (children)[73]
Nasal polyps[127]	Obesity[66]
Height[74]	Smoking[74]
Male sex (potentially confounded by height)[74]	Corticosteroids (inhaled and/or oral)[76]
Consumption of dietary nitrates (including caffeine, lettuce, radishes)	Bronchoconstriction[77]
Rhinovirus in healthy people (inconsistent in patients with asthma)[74]	Early allergic reactions[77]
Morning (diurnal variation)[76]	

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asthma diagnosis, which remains a clinical diagnosis that should always be viewed with clinical context and other objective measurements such as spirometry. Likewise, a single FeNO measurement cannot be interpreted alone, regardless of pretest probability.[54]

The ATS recommends the use of FeNO to support a diagnosis of asthma where objective evidence is needed, particularly in the diagnosis of eosinophilic inflammation.[29] The ATS describes that high FeNO levels (>50 ppb in adults and >35 ppb in children, ►**Table 1**), when interpreted in the clinical context, indicate that eosinophilic inflammation is present with corticosteroid responsiveness in symptomatic patients, while low levels (<25 ppb in adults and <20 ppb in children, ►**Table 1**) make this unlikely and intermediate levels should be interpreted with caution.[29]

Current NICE guidelines, which use lower FeNO cut-off levels than ATS (►**Table 1**), recommend the use of FeNO as part of the diagnostic workup where a diagnosis of asthma is being considered in adults or where there is diagnostic uncertainty in children.[33] FeNO levels are again interpreted in a clinical context and further testing, such as bronchial provocation testing may aid the diagnosis by demonstrating airway hyperresponsiveness.[33] GINA guidelines acknowledge the role of FeNO in identifying eosinophilic inflammation in asthma but do not currently see a role for FeNO in asthma diagnostic algorithms.[1]

A systematic review and meta-analysis of FeNO in the diagnosis of asthma in steroid-naive patients found a diagnostic odds ratio of 9.23 (6.55–13.01). The specificity of the test (0.82, 95% confidence interval [CI]: 0.76 to 0.86) was found to be superior to the sensitivity (0.65, 95%: 0.58–0.72), with FeNO being better at ruling patients in as having asthma rather than ruling them out.[78] A positive FeNO will thus increase the probability of asthma, but a negative FeNO does not exclude it. Meta-regression analyses of the same meta-analysis found higher FeNO cut-off values to be associated with increased specificity but not sensitivity. Age did not affect diagnostic accuracy, but there was variance in sensitivity with FeNO devices.[78]

FeNO can therefore be used to support a diagnosis of asthma and help find evidence of type 2 inflammation; however, not all patients with asthma will have type 2 inflammation and patients with non–type 2 asthma will not have elevated FeNO levels.[51]

Prediction of Future Risk

Understanding future risk is an important component in stratifying patients' treatment.[1] Increased FeNO levels are associated with increased risk of exacerbations,[79–83] poor lung function,[84–86] and accelerated decline in lung function.[87–89] Post hoc analysis of the Liberty Asthma QUEST study, a 52-week phase 3 double-blind randomized parallel-group study evaluating Dupilumab versus placebo in moderate to severe uncontrolled asthma, showed that baseline FeNO in the placebo group was predictive of future exacerbation rate. Subjects with a baseline FeNO of ≥50 ppb had a 1.54 times increased exacerbation rate compared with subjects with a baseline FeNO of <25 ppb (95% CI: 1.11–2.14, $p = 0.0097$), while those with a FeNO ≥25 ppb and <50 ppb had a numerical 1.33 times higher exacerbation rate (95% CI: 0.99–1.78, $p = 0.0572$) compared with those who had a FeNO <25 ppb. High baseline FeNO was particularly associated with an increased risk of exacerbations when combined with elevated blood eosinophils and past exacerbation history. Persons with a FeNO ≥25 ppb, blood eosinophil count ≥150 cells/μL, and ≥2 exacerbations in the preceding year had an exacerbation rate 3.62 times higher than patients with a FeNO <25 ppb, blood eosinophil count <150 cells/μL, and one prior exacerbation (95% CI: 1.67–7.81, $p = 0{\cdot}0011$).[79] A real-life study examining type 2 inflammation biomarkers in unselected patients with asthma found FeNO to be more predictive of exacerbations ($r = 0.42$, 95% CI: 0.19–0.61, $p = 0.0008$) than peripheral blood eosinophils ($r = 0.34$, 95% CI: 0.1–0.6, $p = 0.0078$), but this may be confounded by the relatively high use of OCS and its effects on eosinophils.[80] However, a systematic review found a low FeNO level in ICS-treated asthmatic patients to predict low risk of exacerbations.[81]

An increased FeNO has been associated with worse lung function in both adults[84] and children.[84–86] Raised FeNO with simultaneous blood eosinophils of ≥300 cells/μL were associated with an increased adjusted odds ratio of 2.15 (95% CI: 1.28–3.59) for a forced expiratory volume in 1 second (FEV_1) less than 80% of predicted in 1,419 patients with asthma aged 6 to 79 years from the National Health and Nutrition Examination Survey (NHANES) 2007–2012.[84] In children, a Korean prospective study of 5- to 15-year-olds found a raised FeNO in those with allergic asthma to have a significant negative correlation with FEV/FVC (forced vital capacity) ratio ($r = 0.246$, $p \leq 0.05$) but no significant association with FEV_1% predicted or in nonallergic asthma.[85] FEV_1% predicted was, however, found to be significantly reduced in Latino children aged 6 to 18 years with persistent asthma and a of FeNO ≥ 20 ppb compared with those with a FeNO <20 ppb ($p = 0.001$).[86]

Higher FeNO can also predict accelerated lung function decline.[87–89] A 5-year prospective study of 200 newly diagnosed adults with asthma identified a high FeNO of ≥57 ppb to be an independent predictor of accelerated lung function decline. This was associated with −37.9 mL/year change in post-bronchodilator FEV_1 ($p = 0.015$) and a negative predictive value of 77% but a positive predictive value of only 45%. However, the positive predictive value for accelerated lung function decline was 100% with a FeNO ≥57 ppb and BMI ≤23.05 kg/m^2 combined.[87] A prospective study of Japanese adults with controlled asthma found a FeNO of >40.3 ppb to have a 43% sensitivity and 86% sensitivity to identify patients with an accelerated decline in lung function.[88] The association between FeNO and lung function decline has also been shown over extended time frames. In a prospective multicenter study, based on the first and third surveys in the European Community Respiratory Health Survey, current FeNO levels were compared with percentage lung function decline over the preceding 20 years. Despite relatively low FeNO levels (geometric mean of 21.1 ppb, 95% CI: 20.0–22.3),

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higher percentage declines of FEV_1 and FEV_1/FVC in asthmatic patients were associated with higher FeNO levels ($p = 0.001$ for both).[89]

Predicting Inhaled Corticosteroid Responsiveness

A raised FeNO is indicative of airway inflammation that is likely to respond to ICS.[46,47] An increased response to ICS treatment has been shown with increasing baseline FeNO. This has been used to direct and stratify which asthmatic patients are likely to respond to ICS treatment.[69]

In a randomized cross over trial of mild to moderate asthmatics, ICS therapy resulted in a significant reduction in FeNO, which was greater with the higher dose (fluticasone propionate [FP]: 100 vs. 500 µg) correlating with a change in morning FEV_1 (FP: 100; 0.18 L [95% CI: 0.1–0.26 L], $p = 0.001$) and FP: 500; 0.18 L [95% CI: 0.08–0.29 L], $p = 0.004$), but no significant differences in the evening.[76]

A meta-analysis found a 40% reduction in exacerbations when FeNO-based management was used to tailor asthma therapy.[90] However, the same study did not show a significant difference in asthma control or lung function when incorporating FeNO-based management. Baseline FeNO also impacts on ICS treatment response, in a randomized controlled trial (RCT) of steroid-naive patients; for every 10 ppb increase in baseline FeNO, the change in Asthma Control Questionnaire (ACQ) 7 with ICS increased by 0.071 ($p = 0.044$) compared with placebo.[58] Suggesting the size of the treatment response is related to the FeNO level. Attempts to reduce corticosteroid dose through FeNO measurement have been less successful; a single-blind parallel group RCT using a composite of type 2 biomarkers (including FeNO) to guide treatment did not result in a greater proportion of patients reducing corticosteroid dose versus control, although the lack of response may have been as a result of patients not following the biomarker-driven dose titration algorithm.[91] FeNO can therefore be used to help guide the addition, and appropriate use, of ICS therapy[1,29]; it should not, however, be used to withhold ICS therapy.[1]

Confirming Adherence

Nonadherence is recognized as a major contributing factor in poor asthma control and difficult-to-treat asthma.[92–95] The suppression of FeNO through ICS therapy allows for its use in the monitoring of ICS therapy distinguishing suboptimal adherence from refractory disease, with a persistently raised FeNO a potential indicator of nonadherence.[29,53,69]

One study developed a FeNO suppression test, demonstrating a significant and rapid fall in FeNO after 7 days of directly observed ICS (DOICS) treatment. Patients with difficult-to-treat asthma and an elevated FeNO (>45 ppb) were defined as adherent or nonadherent according to their ICS prescription fillings. Nonadherent patients demonstrated a greater reduction in FeNO from baseline (79 ppb ± 26%, $p = 0.003$) than adherent subjects (47 ppb ± 21%) after 7 days of DOICS with changes evident from 5 days ($p = 0.02$).[69] This study led to the development of the "FeNO suppression test." More recently, the FeNO suppression test was used to examine the use of remote monitoring in routing clinical care in severe asthma centers of the United Kingdom. Those patients with a positive FeNO suppression test, when adherent to ICS/long-acting β2-adrenergic receptor agonist treatment, had improved short-term outcomes compared with a negative test, including a significantly greater change in FEV_1% (mean, 88.2 ± 16.4 vs. 74.1 ± 20.9; $p < 0.01$).[53]

Raised FeNO with a positive FeNO suppression test demonstrates corticosteroid responsiveness and can reveal nonadherence; however, it is important to note that approximately one-third of patients have raised FeNO levels that are resistant to corticosteroid therapy.[53,69] FeNO, therefore, also provides a useful tool to identify and study relative corticosteroid resistance in severe asthma.[96]

Personalizing Biologic Choice

Poorly controlled severe asthma has a significant healthcare burden[97,98] and there are several monoclonal antibodies, all of which target type 2 pathways, licensed as add-on therapy in severe asthma.[19–23] The use of biomarkers, including FeNO, can help personalize treatment for those who are likely to respond.[11,26,27,99]

The first biologic therapy to be licensed as an add-on therapy for severe persistent and uncontrolled allergic asthma, Omalizumab, is an anti-IgE monoclonal antibody, which is approved in patients ≥6 years old.[100] The EXTRA study used a prespecified post hoc analysis to evaluate the effects of FeNO levels on Omalizumab response.[101] Patients were assigned to a FeNO-low (<19.5 ppb) or FeNO-high (≥19.5 ppb) subgroup according to their baseline readings. There was a 53% (95% CI: 37–70; $p = 0.001$) reduction in exacerbations for the Omalizumab-treated versus placebo group in the FeNO-high subgroup, compared with a 16% (95% CI: −32 to 46; $p = 0.45$) reduction in the FeNO-low subgroup after 48 weeks of treatment.[101] However, a large observational study of Omalizumab found a positive response in 87% of subjects (according to clinical exacerbation rate, lung function, or ACT scores) regardless of FeNO level.[102] The role of FeNO as a biomarker for Omalizumab therefore remains unclear.[54]

As previously discussed, FeNO is mediated via IL-13 signaling, while eosinophils are mediated by IL-5. Anti-IL-5 (mepolizumab[20,103] and reslizumab[23]) and anti-IL-5 receptor (benralizumab[21]) antibodies are approved as add-on therapy in severe refractory eosinophilic asthma[1] in adults and for mepolizumab in children aged ≥6 years.[1,57] Initial trials showed that the three therapies reduce exacerbations with a concurrent fall in blood eosinophils but did not show a significant fall in FeNO levels. Nor did it show FeNO, unlike blood eosinophils, to be a predictor of response.[103–105] However, a post hoc analysis of the phase 2b DREAM study found mepolizumab treatment in patients with a high FeNO (≥25 ppb) and raised blood eosinophils (≥300 cells/µL) to have a greater reduction in exacerbations rate than those

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with low FeNO (<25 ppb) and raised blood eosinophils (62 vs. 34%). There was no significant change in exacerbation rate with Mepolizumab and low blood eosinophils (<300 cells/μL) regardless of FeNO.[106] Furthermore, a recent real-world retrospective study found subjects with a very high baseline FeNO (≥75 ppb) had a significant fall in their FeNO levels from 100 ppb (interquartile range [IQR], 88–145) to 58 ppb (IQR, 33–102) after 1 year of benralizumab treatment ($p < 0.001$),[107] suggesting that IL-5R expressing cells, including eosinophils and basophils, may be an important source of IL-13.[107,108]

FeNO is recognized to result as a consequence of IL-13-driven inflammation and this is demonstrated in its response to dupilumab therapy, an anti-interleukin-4 (IL-4)-α receptor monoclonal antibody, which blocks both IL-4 and IL-13 signaling.[109] It has been shown, in a phase 2b dose ranging clinical trial, to result in a significant and sustained reduction in FeNO alongside reductions in other type 2 biomarkers such as IgE.[110] There was a transient rise in blood eosinophils.[110] Prespecified subgroup analysis from a phase 3 trial showed raised baseline FeNO levels (≥25 ppb) to be predictive of lowering exacerbation rates and increase in FEV_1.[22] The magnitude of baseline FeNO was also significant; for example, with respect to FEV_1 change from baseline, patients with a high FeNO (≥50 ppb) on 300 mg of dupilumab showed an improvement of 0.39 L (95% CI: 0.26–0.52) as compared with matched placebo, while those with an intermediate FeNO (≥25 to <50 ppb) showed an improvement of 0.12 L (95% CI: 0.03–0.21) compared with matched placebo.[22] These results have been mirrored in a further phase 3 trial of adults and adolescents dependent on maintenance OCS.[111] Dupilumab treatment once again reduced FeNO levels by week 2 in combination with a significant reduction in oral glucocorticoid use. Reduction in exacerbation rate and improvement in FEV_1 were also more pronounced with a raised FeNO and/or eosinophil count.[111]

Tezepelumab, a human monoclonal antibody that blocks thymic stromal lymphopoietin, in both the PATHWAY and NAVIGATOR trials, resulted in reduced exacerbation rates and improved lung function with a simultaneous and sustained reduction in FeNO and blood eosinophils alongside a gradual decline in IgE over the 52 weeks.[34,112] In the phase 3 NAVIGATOR study, tezepelumab administration led to a fall in blood eosinophil and FeNO levels by the second week and was sustained throughout the 52 weeks of the trial. A reduction in exacerbation rate was seen independent of blood eosinophils or FeNO. However, the reduction in annualized exacerbations with treatment was more pronounced with a high (≥25 ppb) baseline FeNO. Treatment with tezepelumab resulted in an exacerbation rate ratio of 0.68 (95% CI: 0.51–0.92) for subjects with a baseline FeNO <25 ppb, decreasing to 0.32 (95% CI: 0.25–0.42) with a high baseline FeNO compared with placebo. This simultaneous reduction in FeNO, blood eosinophils, and IgE suggest that tezepelumab suppresses multiple inflammatory pathways and may have a broader effect than targeting individual type 2 cytokines.

Cost-Effectiveness and Limitations

Asthma is associated with significant direct and indirect healthcare costs with the highest proportion due to uncontrolled asthma.[97,113] Using FeNO as part of clinical pathways has been shown to be a cost-effective tool in reducing these costs.[56,114–120] Appropriate diagnosis of asthma has substantial cost as well as health implications.[4,8] The use of FeNO testing in conjunction with existing tests is considered by NICE in the United Kingdom to be more cost-effective than the existing tests alone and is recommended as an option to aid diagnosis in adults and children.[33,114] They calculate FeNO with bronchodilator reversibility testing to have a quality-adjusted life year (QALY) gain of 4.2829 with an incremental cost-effectiveness ratio (ICER) of £686.08 to £688.33 per QALY gained depending on the device used. This contrasts with methacholine airway hyperresponsiveness testing, which gained the highest QALY but was only 0.005 greater and was associated with an ICER of £1.125 million per QALY gained. All other diagnostic options had significantly lower QALYs.[114]

The use of FeNO to promote asthma control has also been shown to be cost-effective. In the primary care setting, a cluster RCT demonstrated a FeNO-driven control strategy, incorporating Asthma Control Questionnaire (ACQ) 7 scoring, reduced medication, and was cost-effective while maintaining asthma control and quality of life. This approach resulted in an 86% probability of cost-effectiveness when set at $50,000/QALY. This was significantly higher compared with a symptom score strategy which had a 2% probability for partially controlled asthma (ACQ score <1.5) and 12% for controlled asthma (ACQ 7 score <0.75).[118] In the real-world context, Arnold et al used retrospective case-crossover analysis of asthma-related claims from the Medicare database to analyze the effect of FeNO testing as part of asthma management. It found that emergency department and inpatient attendances for asthma dropped from 97% in the year before FeNO testing to 46% during the FeNO period, resulting in a drop in daily asthma-related charges from $16.21 to $6.46 during the FeNO period ($p = 0.0133$).[116]

FeNO does, however, have upfront and ongoing costs associated with machine and filter purchase,[114] which can result in variable and difficult access to testing. While, for example, FeNO testing is available throughout specialist services in the United Kingdom, globally it is not widely used and reimbursement is not supported in some countries.[54]

Limitations

FeNO is a marker of type 2 inflammation and therefore has less of a role in the diagnosis of non–type 2 asthma.[51] Even within type 2 asthma, the independent but complementary pathways that result in raised FeNO levels and eosinophilia means that FeNO levels will not always reflect the level of eosinophilic inflammation in the airways.[96] Levels also differ among individuals and over time and this has led to difficulties in establishing cut-offs for "high" and "low" values.

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Guideline development has provided some standardization; however, these differ between guidance (►**Table 1**) and the disparities have led to problems interpreting research.[78] Furthermore, there are several confounders, as discussed in the "Interpretation of FeNO Values" section, which can increase or decrease FeNO levels[74] (►**Table 2**). The lack of an evidence base for patient-adjusted FeNO cut-offs has been cited as the remaining issue in the clinical use of FeNO.[121] However, this is being addressed through a joint ERS–Global Lung Function Initiative task force who are developing subject-specific FeNO values[122] similar to those used in spirometry.[123] Guidelines and research thus stress the importance of using FeNO in conjunction with clinical history and investigations such as lung function. To gain a further understanding of this in severe asthma, the RASP-UK consortium is currently researching the role of combining biomarkers such as blood eosinophils and FeNO and corticosteroid therapy response.[91,124]

FeNO is recommended as an adjunct in asthma diagnosis by both ATS[29] and NICE[114] but is still not recommended by GINA in their diagnostic pathway.[1] This can impact FeNO testing reimbursement and availability with testing often being limited globally.[54] In some countries, such as the United Kingdom, FeNO is available in specialist centers but is often unavailable in primary care where the majority of asthma diagnoses are made[125] leading to calls for increased education on the role and importance of FeNO measurement in asthma management.[54]

Conclusion

Asthma diagnosis and management is traditionally based on symptoms. Measurement of FeNO, which is increased in many patients with asthma, offers an objective measure of airway inflammation secondary to type 2 pathways, therefore providing an additional biomarker in the diagnosis and management of type 2 asthma. The proinflammatory cytokine IL-13 drives increased FeNO levels, which provide a reflection of current airway inflammation. FeNO levels have been shown to predict blood and sputum eosinophils but are not synonymous and they should be used in combination rather than as a replacement. FeNO levels increase diagnostic accuracy in asthma and can be used to predict response to ICS. The suppression of FeNO with ICS therapy also allows for it to be used to guide corticosteroid therapy and monitor its adherence. Additionally, a raised FeNO can be used to stratify future risk to patients and correlates with increased exacerbation rates and accelerated decline in lung function. FeNO levels can also be used to identify patients who may benefit from some of the available biologic therapies and to monitor the response to treatment. FeNO testing is easy to use and cost-effective, provides results at the point of access, and is noninvasive. Applicability and use have increased with standardized cut-off values; however, these values vary between guidance, and this has caused difficulty with adoption and interpretation of research into the FeNO's clinical utility. Further understanding is also needed on the additive role of combining FeNO with other biomarkers, such as blood eosinophils.

In conclusion, FeNO, acting as a biomarker of current airway inflammation, provides an opportunity to tailor asthma treatment, increasing diagnostic accuracy and optimizing management in type 2 asthma. While its ease of use and cost-effectiveness has led to its increased use, further research into the clinical utility of FeNO, alongside increased access, is needed if we are to fully harness its potential in advancing personalized asthma therapy.

Conflict of Interest
A.M.-G. has attended advisory boards for GlaxoSmithKline, Novartis, AstraZeneca, Teva, and Sanofi; has received speaker fees from Novartis, AstraZeneca, Sanofi, and Teva; has participated in research for which his host institution has been remunerated with AstraZeneca; has attended international conferences sponsored by Teva; and has consultancy agreements with AstraZeneca and Sanofi.
L.L. has no conflicts of interests to declare.

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